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Influence of nutrients on cardiac autonomic function in nondiabetic overweight subjects

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Abstract

The current study sought to determine whether there is a link between cardiac autonomic dysfunction and food intake in overweight subjects. One hundred five nondiabetic overweight (body mass index >27 kg/m^2) subjects were studied. Heart rate variations were analyzed during 3 bedside standard tests investigating mainly vagal control: deep breathing, lying-to-standing, and Valsalva tests. The resting metabolic rate and substrate oxidation rates were measured by indirect calorimetry. Dietary intake was estimated from a 3-day recall of food intake. Cardiac parasympathetic dysfunction (PSD) was found in 39 subjects. The sex ratio, age, anthropometric parameters, biochemical parameters and insulin resistance index, resting metabolic rate, and substrate oxidation rates did not differ in the subjects with or without PSD. The total 24-hour energy intake was similar, but the carbohydrate intake was significantly higher in the subjects with PSD (P = .006), and the fat and protein intakes were significantly lower (P = .026 and .045, respectively). In the logistic regression analyses, PSD correlated with carbohydrate and fat intake, independently of serum insulin levels. Glucose oxidation rate correlated negatively with fasting and postglucose serum insulin levels only in the subjects with PSD (P = .006 and .005, respectively). Cardiac parasympathetic dysfunction is associated with higher carbohydrate intake and lower fat and protein intakes in overweight subjects. A sympathetic override may contribute to reducing the glucose oxidation rate in subjects with PSD.

1. Introduction

Impairment of cardiac autonomic function is frequent in nondiabetic obese subjects. Parasympathetic control of heart rate variations (HRVs) during bedside standard tests (Valsalva, deep breathing, and lying-to-standing) is impaired in 40% of them [1]. Similarly, the high frequency peak provided by the spectral analysis of HRVs, which accounts for vagal cardiac activity, is reduced in obese subjects [2]. There is also some evidence of impairment of vascular sympathetic activity: the hemodynamic response to the handgrip test may be reduced [3] as well as the peripheral vasoconstrictive response to sympathetic activation [4].

Some data suggest that cardiac parasympathetic dysfunction (PSD) is associated with a more severe insulin resistance in nondiabetic obese subjects and type 2 diabetic patients [5-7]. A 10-year follow-up study of newly diagnosed type 2 diabetic patients has shown that high insulin levels seem to be predictive of the development of cardiac PSD irrespective of obesity and glycemia [8]. In addition, nutrient intake may affect autonomic nervous system activity. Fasting suppresses the activity of the sympathetic nervous system (SNS) [9], whereas overfeeding a mixed diet stimulates sympathetic activity in rats. Carbohydrate (glucose, sucrose, and fructose) [10-12] and fat (lard) [13] activate sympathetic activity even when total energy intake is not increased. The potential role of insulin in mediating the SNS stimulation associated with carbohydrate administration is widely accepted. Experiments on the isocaloric substitution of sucrose or glucose for casein showing enhanced SNS activity in rats fed a low-protein diet suggest that carbohydrates stimulate the SNS to a greater extent than protein and lard [14-16]. Sympathetic activation by dietary fat varies among different fats, suggesting the role of fatty acid intake in dietary regulation of the SNS [17].

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The thermic effect of protein has been shown to be inhibited by atropine, phentolamine, or prazosin but not by propranolol, which suggests that the parasympathetic nervous system and the SNS via α_1-adrenoceptors are involved in the thermic effect of protein [12]. The thermic effect of carbohydrates is lower than that induced by protein and is inhibited by propranolol but not by phentolamine or atropine, which suggests that the SNS via β-adrenoceptors, but not the parasympathetic nervous system, contributes to the thermic effect of carbohydrates [12]. Thus, the autonomic nervous system is involved in the thermic effect of protein and carbohydrates via different mechanisms.

The aim of the present study was to determine in a cross-sectional study on overweight subjects whether there is a link between cardiac autonomic dysfunction and food intake.

2. Subjects and methods

2.1. Subjects

One hundred five consecutive nondiabetic overweight subjects, aged 42.7 ± 1.2 years (17-72 years), with a body mass index (BMI) greater than 27 kg/m^2 were included. There were 92 women and 13 men. All of them were normotensive and free of cardiac, respiratory, hepatic, renal, or blood disorders, and none of them were taking any treatment likely to change heart rate or blood pressure. None had symptoms of autonomic or peripheral neuropathy. The standard 12-lead electrocardiogram was normal.

All the subjects were investigated before the beginning of our weight-loss program, and no such program had been carried out within the 3 months before this study. They slept Sunday night in our department, and all the investigations were performed on Monday. First, respiratory exchanges were measured, then an oral glucose tolerance test was performed, and the cardiac autonomic function tests were carried out between 11:30 and 1:00 PM. Body composition measurements and the dietary recall were performed in the afternoon.

2.2. Methods

2.2.1. Respiratory exchange measurements

Energy expenditure was measured by indirect calorimetry, under carefully standardized conditions. The subjects were asked to refrain from smoking and drinking alcohol at least 12 hours before the test procedure. The night before the investigation, they slept in our metabolic unit, where the ambient temperature was between 22°C and 24°C to ensure basal conditions. They fasted overnight and, after voiding, remained in a semirecumbent position until the measurements were completed in the metabolic unit.

Continuous respiratory measurements were begun at 7.30 AM and maintained for 1 hour before oral intake of glucose. Measurements were averaged over the last 30 minutes. Indirect calorimetry measurements were performed by using a continuous open-circuit ventilated-hood system (Deltatrac Monitor MBM-100, Datex Instrumentarium Corp, Helsinki, Finland). A calibration of oxygen, carbon dioxide, and airflow was carried out with reference gas before the beginning of the test. The oxygen and carbon dioxide concentrations were continuously measured, with the mean values of carbon dioxide production and oxygen consumption calculated for each 1-minute interval. The resting metabolic rate (RMR) and glucose, lipid, and protein oxidation rates were determined as previously described [18].

2.2.2. Cardiac autonomic function tests

HRVs were studied during 3 bedside standard tests investigating mainly vagal control: deep breathing, lying-to-standing, and Valsalva tests, as previously described [1,3,19]. HRVs were assessed by computerized analysis using the Autocaft system (UnivEd Technologies Ltd, Edinburgh, UK) [20]. Briefly:

- The deep breathing test consisted of 6 deep respiratory cycles in 1 minute in the recumbent position. The result was expressed as the mean value for the ratio of maximal R-R (interval between 2 consecutive R waves on ECG recording) during breathing out to minimal R-R during breathing in at each respiratory cycle.
- For the lying-to-standing test, the patients were asked to remain lying for 1 minute and then to stand up quickly. The result was expressed as the ratio of the longest R-R interval (approximately the 30th beat after standing up) to the shortest R-R interval (approximately the 15th beat).
- The Valsalva test was carried out with the subjects seated. They were asked to exhale a deep breath to maintain 40 mm Hg pressure for 15 seconds. The Valsalva test was performed 3 times consecutively, and the mean value for the Valsalva ratio defined by the longest R-R interval after breathing out/the shortest R-R interval while breathing out was calculated.

We have previously shown that the reproducibility of these tests is good [21].

The influence of age on HRV during these tests has been demonstrated. For each test, results were interpreted taking age into account and considering as abnormal a result below the fifth percentile line of the correlation between age and HRV defined in a published series of normal controls [22]. Cardiac PSD was defined by at least 1 abnormal test.

2.2.3. Body composition

Fat-free mass (FFM) and fat mass (FM) were measured by bioelectric impedance analysis using a double-frequency device, respectively, 5 kHz and 1 MHz, and 4 subcutaneous electrodes (IMP B01; l'Impulsion, Caen, France) [23].

2.2.4. Analytical procedures

Plasma glucose and serum insulin were measured at fasting and 120 minutes after 75 g of glucose was taken orally. Plasma glucose determination was performed at the routine

laboratory using the hexokinase method. Serum fructosamine was measured by a colorimetric method using tetrazolium blue (Roche Diagnostic System, Neuilly/Seine, France) and HbA1c by microcolumn chromatography. Serum insulin was measured by radioimmunoassay (Behring, Mahrburg, Germany) with mean interassay and intra-assay coefficients of variation of less than 10%. The insulin resistance index was calculated by the homeostasis model assessment method [24]. Serum total cholesterol, triglycerides, and high-density lipoprotein fraction were measured at fasting, and low-density lipoprotein cholesterol was calculated according to the Friedewald formula. The urine nitrogen content was determined by chemiluminescence [25].

2.2.5. Dietary intake

Dietary intake was evaluated according to data obtained from dietary questionnaires. The 3-day recall technique was used, for 3 days of the previous week, Thursday to Saturday. Total energy intake and macronutrient intakes were calculated by using a dietetic software (Bilnut 3, Nutrisoft, Cerelles, France) whose dietary database is made up of 610 foods.

2.2.6. Statistical analyses

Results are expressed as mean ± SEM values. Between-groups comparisons for continuous variables were performed by variance analysis or the Kruskal-Wallis test as appropriate according to the Gaussian or non-Gaussian distribution of the data. Linear or nonparametric correlations were calculated between 2 sets of quantitative data, and percentages were compared by χ^2 and Fisher exact tests. Logistic regression models were used to find out the independent determinants of PSD. General linear models were used to compare the slopes of the regression lines between quantitative parameters in different groups and to compare mean values of quantitative parameters after age adjustment. Statistical analyses were carried out with the SPSS Release 6.0 package (SPSS Inc, Chicago, Ill) on a PC device.

Table 1
Clinical characteristics of the subjects with or without cardiac PSD

	PSD	No PSD	*P*
n	39	66	
Sex ratio (male/female)	4/35	9/57	.428
Age (y)	42.8 ± 2.2	42.6 ± 1.5	.945
Height (m)	1.63 ± 0.01	1.63 ± 0.01	.911
Weight (kg)	96.5 ± 3.4	89.6 ± 2.5	.101
BMI (kg/m^2)	36.3 ± 1.2	33.9 ± 0.9	.101
Waist circumference (cm)	102.6 ± 2.9	99.7 ± 1.9	.370
Hip circumference (cm)	118.3 ± 2.1	115.0 ± 1.3	.166
Waist/hip	0.87 ± 0.02	0.87 ± 0.01	.887
% Fat mass	37.7 ± 1.1	37.8 ± 0.7	.926
Heart rate (bpm)	72.5 ± 1.6	70.1 ± 1.1	.199
Systolic blood pressure (mm Hg)	130 ± 3	131 ± 2	.837
Diastolic blood pressure (mm Hg)	77 ± 2	77 ± 1	.979
Deep breathing	1.25 ± 0.05	1.38 ± 0.03	.026
Lying-to-standing	1.20 ± 0.04	1.29 ± 0.03	.050
Valsalva	1.38 ± 0.04	1.52 ± 0.03	.013

bpm indicates beats per minute.

Table 2
Biologic parameters in the subjects with or without cardiac PSD

	PSD	No PSD	*P*
n	39	66	
Blood glucose (mmol/L)			
Fasting	5.05 ± 0.16	5.04 ± 0.09	.964
After glucose	7.13 ± 0.39	6.90 ± 0.53	.939
Serum insulin (pmol/L)			
Fasting	90 ± 6	84 ± 4	.377
After glucose	437 ± 59	454 ± 41	.814
Hemoglobin (g/dL)	12.9 ± 1.8	13.2 ± 1.1	.094
HbA1c (%)	5.44 ± 0.15	5.20 ± 0.09	.175
Fructosamine (μmol/L)	212 ± 5	210 ± 4	.789
Insulin resistance index	2.87 ± 0.23	2.63 ± 0.14	.353
Total cholesterol (mmol/L)	5.26 ± 0.15	5.35 ± 0.13	.667
HDL cholesterol (mmol/L)	1.32 ± 0.06	1.46 ± 0.05	.098
LDL cholesterol (mmol/L)	3.31 ± 0.14	3.31 ± 0.13	.998
Triglycerides (mmol/L)	1.81 ± 0.20	1.48 ± 0.08	.090
Uric acid (μmol/L)	287 ± 11	291 ± 10	.832
Creatinine (μmol/L)	79.9 ± 2.0	78.9 ± 1.3	.679

HDL indicates high-density lipoprotein; LDL, low-density lipoprotein.

3. Results

3.1. Cardiac autonomic function tests

HRV during the deep breathing and Valsalva tests correlated negatively with age (P = .028 and .003, respectively). Taking age into account, 39 overweight subjects had at least 1 abnormal test as compared with the control series [22]: 29 had mild PSD (1 abnormal test), and 10 had confirmed PSD (2 abnormal tests).

In the group with PSD (39 subjects), HRVs during the 3 standard tests were, as expected, significantly lower than in the group free of PSD (66 subjects) (Table 1).

Table 3
RMR and substrate oxidation rates as provided by indirect calorimetry, and energy intakes in the subjects with or without cardiac PSD

	PSD	No PSD	*P*
N	39	66	
RMR (MJ/24 h)	7.30 ± 0.18	7.09 ± 0.16	.415
RMR/FFM (kJ/kg per 24 h)	170.1 ± 8.8	164.7 ± 6.7	.644
Oxidation rates (mg/kg per min)			
Glucose	0.95 ± 0.10	0.98 ± 0.10	.827
Lipid	0.73 ± 0.05	0.75 ± 0.05	.800
Energy intakes			
Total (MJ/24 h)	7.61 ± 0.39	8.27 ± 0.44	.131
Carbohydrates[a]	48.3 ± 1.1	44.1 ± 1.0	.006
Fat[a]	34.2 ± 1.0	37.0 ± 0.8	.026
Protein[a]	17.9 ± 0.6	19.6 ± 0.6	.045
Fatty acid intake (% of total fat)			
Saturated	46.2 ± 1.2	47.2 ± 0.9	.520
Monounsaturated	37.7 ± 0.8	37.3 ± 0.6	.673
Polyunsaturated	16.4 ± 1.4	15.5 ± 1.0	.608

[a] Expressed as % of total energy intake.

Table 4
Logistic regression analyses with cardiac PSD as dependent variable

	Carbohydrates intake	Fat intake	Fasting insulinemia	120-min Insulinemia
1	1.086 (1.022-1.154) *.008*		1.006 (0.994-1.019) NS	
2	1.084 (1.021-1.151) *.008*			0.999 (0.998-1.001) NS
3		0.926 (0.863-0.993) *.031*	1.005 (0.993-1.017) NS	
4		0.926 (0.863-0.993) *.031*		0.999 (0.998-1.001) NS

Carbohydrate intake (% of total energy intake) and serum insulin at fasting or 120 minutes after oral glucose challenge were considered as independent variables in the first and second analyses. Carbohydrate intake was replaced by fat intake (% of total energy intake) in the third and fourth analyses. Odds ratios are given with their 95% confidence intervals in parentheses and *P* values in italics. NS indicates not significant.

3.2. Correlates of cardiac PSD

The sex ratio, mean age, body weight, BMI, waist/hip ratio, FM, and FFM, heart rate, and blood pressure and biochemical parameters including insulin resistance index did not differ significantly in subjects with PSD compared with those with normal autonomic function tests (Tables 1 and 2). RMR and substrate oxidation rates were also very similar in the 2 groups (Table 3). Similarly, comparisons of these parameters in women with or without PSD did not disclose any significant difference.

In the subjects with PSD compared with those without PSD, the total 24-hour energy intake was similar. Expressed as the percentages of total 24-hour energy intake, the carbohydrate intake was significantly higher in the subjects with PSD ($P = .006$), and the fat and protein intakes were significantly lower ($P = .026$ and .045, respectively) (Table 3).When taking each cardiac autonomic function test separately, after adjustment for age, there was a trend to lower HRV levels in the subjects in the higher tertile of carbohydrate intake (as percentage of total 24-hour energy intake) than in those in the lower tertile, the difference being significant ($P = .035$) for the deep-breathing test.

HRVs during the 3 autonomic tests were plotted against serum insulin at fasting and 120 minutes after glucose challenge. HRV during the lying-to-standing test correlated negatively with serum insulin 120 minutes after oral glucose challenge ($r = -0.231$; $P = .020$). The correlation was still significant after controlling for age ($r = -0.233$; $P = .020$).

Logistic regression analyses were carried out, taking PSD as a dependent variable and macronutrient intakes and insulin levels as independent variables. With carbohydrate intake (% of total energy intake) and serum insulin at fasting or after glucose as independent variables, PSD correlated only with carbohydrate intake. When replacing carbohydrate by fat intake (% of total energy intake), PSD correlated only with fat intake (Table 4).

The glucose oxidation rate correlated negatively with serum insulin 120 minutes after oral glucose challenge ($r = -0.295$; $P = .003$). In the PSD group, but not in the group free of PSD, the glucose oxidation rate correlated negatively with serum insulin at fasting ($r = -0.458$; $P = .006$) and 120 minutes after oral glucose challenge ($r = -0.461$; $P = .005$), and the lipid oxidation rate correlated positively with serum insulin after glucose ($r = 0.440$; $P = .008$). The slope of the regression line between the glucose oxidation

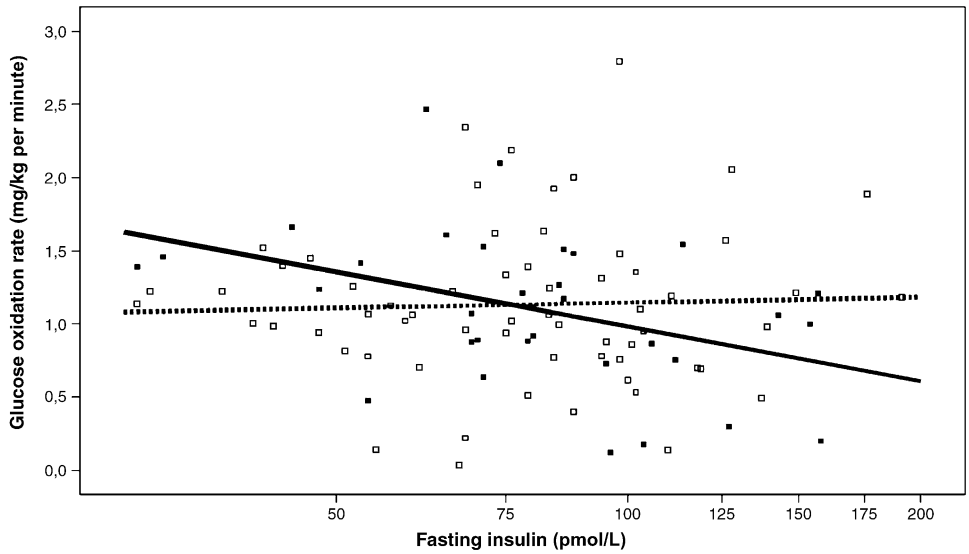

Fig. 1. Regression between glucose oxidation rate and serum insulin at fasting in the groups with (■) or without (□) cardiac PSD. Serum insulin levels are log-transformed. In the PSD group, the slope of the regression line (—) was −1.23 (95% confidence interval −2.16 to −0.31), significantly different from 0 ($P = .01$). In the group without PSD, the slope of the regression line (···) was 0.12 (95% confidence interval −0.68 to −0.93), not significantly different from 0 ($P = .76$).

rate and fasting insulin was null in the group free of PSD and differed significantly in the PSD group ($P = .033$) (Fig. 1). The slopes of the regression lines between the glucose oxidation rate and insulin after glucose, and between the lipid oxidation rate and insulin at fasting or after glucose, did not differ significantly in the 2 groups.

4. Discussion

Cardiovascular autonomic dysfunction is a disorder frequently found in obese subjects. It consists of an impairment of the parasympathetic control of HRVs [1,2], and also of an abnormal cardiovascular response to sympathetic activation [3,4]. Whether it is a complication of obesity or a disorder preceding weight gain is not clearly determined. However, some data suggest that weight gain and maintenance may be associated with a decline in parasympathetic activity [26,27]. In the present study, 3 standard tests were used to analyze HRVs mainly under vagal control. The results showed PSD in approximately 40% of the nondiabetic obese subjects, which confirm our previous data [1]. The principal original finding of this cross-sectional study is that long-term macronutrient intakes are associated with PSD. Patients with PSD had a higher level of carbohydrate intake (as expressed as percentage of total 24-hour energy intake) and lower levels of fat and protein intakes.

Previous studies have suggested that PSD may be associated with a more severe level of insulin resistance [5-7]. Three mechanisms might account for this association [8]. First, the high insulin level or insulin resistance per se could have an effect on autonomic nervous tissues at any level of the reflex arc. Indeed, insulin may increase the activity of the SNS [28,29], and concomitantly the parasympathetic nervous function could be slowed down [30]. Second, a deterioration of the microcirculation in many tissues, which has been associated with insulin resistance [31,32], could lead to neural ischemia. Third, a damage of autonomic nerve endings at the organ level, that is, in the heart muscle or artery walls, may be involved. Such a damage of sympathetic nerve endings in the diabetic heart, which has been shown even in the absence of clinical autonomic neuropathy [33,34], could also affect the vagal system. However, in the present study, the patients with PSD and those without had strictly similar BMI, waist/hip ratio, FM, and FFM and did not differ according to the insulin resistance index provided by the homeostasis model assessment method. There was only a trend (not significant) toward higher fasting serum insulin levels in the patients with PSD.

The logistic regression analyses showed clearly that PSD correlates with macronutrient intakes independently of insulin resistance. Many experimental studies in rats have shown that the activities of the sympathetic and parasympathetic nervous systems are dependent upon diet composition even when total energy intake is unchanged. Protein intake induces activation of both systems, whereas carbohydrates such as glucose, sucrose and fructose, and fat enhance SNS activity [12,13]. Similarly, in humans, glucose and saccharose intake induces SNS activation [11] which is likely to result mainly from insulin response because, during euglycemic-hyperinsulinemic clamp studies, insulin per se activates SNS [35]. The present results showing different nutrient intakes in the overweight subjects with or without PSD are consistent with the experimental data. Indeed, when protein intake is lower independently of changes in total energy intake, cardiac parasympathetic activity is altered. Higher carbohydrate intakes are also associated with lower cardiac parasympathetic activity or indirectly with the relative preponderance of sympathetic activity. Whether this results from a direct effect or indirectly through a relative sympathetic overriding remains to be clarified. In addition, the association between PSD and nutrient intakes may mean an inverse relationship; that is, the relative sympathetic override may influence eating style, in particular may lead to an increase in carbohydrate intake.

Changes in autonomic nervous system activity induced by diet may account for a major part of the various thermic effect of nutrients. Both sympathetic and parasympathetic activations are involved in the thermic effect of proteins, whereas only sympathetic activation seems to be involved in the thermic effect of carbohydrates [12]. In the present study, PSD was not associated with different RMR levels nor with different levels of substrate oxidation rates. However, a negative correlation was found only in PSD subjects between the glucose oxidation rate and the fasting and postglucose-load serum insulin levels. This suggests that PSD may play a role in the previously reported reduction of glucose metabolism associated with insulin resistance in obese subjects. The present data are also consistent with factors which antagonize insulin effects in subjects with PSD. A higher sympathetic activity is likely to be involved in this phenomenon. The pattern seems to be the opposite after glucose intake. Indeed, in obese subjects, we have previously shown that PSD was associated with a stronger inhibition of lipid oxidation after glucose intake which might result from a lower glucose-induced sympathetic activation [36].

The poor prognosis related to severe cardiac PSD is clearly suggested by several follow-up studies in diabetic patients [37,38]. The prognostic value of cardiac autonomic dysfunction in nondiabetic obese subjects remains to be determined. However, mixed meal ingestion induces sympathetic and parasympathetic activation [39-41] which may not be the case in patients with autonomic dysfunction [39]. The QTc interval is lengthened after meal intake, and the autonomic nervous system may play a role in these changes in healthy subjects [40] as has been shown in diabetic patients [41]. Such changes in QTc could cause arrhythmia. They need to be studied in the overweight subjects with PSD, and whether nutrients may induce various QTc changes according to their nature remains to be elucidated.

A decrease in parasympathetic activity and a rise in sympathetic activity, as induced by carbohydrates, may also contribute to hypertension in obese subjects [11,42].

4.1. Limitations of the study

(1) This is a cross-sectional study, and a 3-day dietary recall was the sole measure of macronutrient intake. The differences in carbohydrate intake between the overweight subjects with or without PSD are relatively modest (48.3% vs 44.1% in means). The relationship between long-term carbohydrate intake and cardiac PSD needs to be confirmed in a controlled trial.

(2) There was a marked female preponderance in our study population, and the present findings might be limited to women.

(3) HRVs during the 3 standard tests we used depend mainly on vagal control. However, spectral analysis of HRV can provide a more specific estimate of cardiac vagal activity.

In conclusion, cardiac PSD is frequently found in nondiabetic obese subjects, and this disorder is associated with higher carbohydrate intake and lower fat and protein intakes. These data are in agreement with experimental studies. However, a long-term controlled trial testing higher and lower carbohydrate intake for several weeks is needed to establish causative evidence in normal and obese subjects and to demonstrate the role played by parasympathetic activity as a significant regulator of nutrient partitioning, with possible differences between insulin-resistant and non–insulin-resistant individuals. The clinical relevance of this study is based on the poor prognostic value related to cardiac autonomic dysfunction.

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